

(18)



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

(11) Publication number:

**0 339 465  
A2**

(12)

## EUROPEAN PATENT APPLICATION

(21) Application number: 89107040.1

(51) Int. Cl.<sup>4</sup>: **A61K 31/545 , A61K 31/715 ,  
//(A61K31/715,31:545)**

(22) Date of filing: 19.04.89

Claims for the following Contracting State: ES.

(30) Priority: 19.04.88 JP 94643/88

(43) Date of publication of application:  
02.11.89 Bulletin 89/44

(84) Designated Contracting States:  
**AT BE CH DE ES FR GB IT LI NL SE**

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(54) **Antibacterial composition for oral administration.**

(57) An antibacterial composition for oral administration comprising pivaloyloxymethyl-(6R,7R)-7[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamide]-3-[(Z)-2-(4-methylthiazol-5-yl)-ethenyl]cephem-4-carboxylate,  $\beta$ -cyclodextrin and a pharmaceutically acceptable carrier is disclosed. The addition of  $\beta$ -cyclodextrin remarkably improves the dispersibility of the substance ME1207 to thereby promote the absorption of the same. Thus, the absorbability of the substance ME1207 administered at a hungry state is elevated to a level comparable to that achieved by administering the same after meals.

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## ANTIBACTERIAL COMPOSITION FOR ORAL ADMINISTRATION

FIELD OF THE INVENTION

This invention relates to an antibacterial composition for oral administration containing  
 5 pivaloyloxymethyl-(6R,7R)-7[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamide]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]cephem-4-carboxylate (hereinafter referred to as the substance ME1207),  $\beta$ -cyclodextrin and a pharmaceutically acceptable carrier.

BACKGROUND OF THE INVENTION

The substance ME1207 is a cephem antibiotic for internal use and is a prodrug which is absorbed through the intestine when orally administered and hydrolyzed by esterase present at the intestinal wall to thereby give (6R,7R)-7[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamide]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]cephem-4-carboxylic acid (hereinafter referred to as the substance ME1206) having an antibacterial activity. This substance ME1206 has a wide antibacterial spectrum against gram-positive and gram-negative bacteria and is highly useful in the treatment and prevention of bacterial infectious diseases (cf. EP-A-175610).

20 However, the substance ME1207 has a serious disadvantage that, when orally administered at a hungry state in the form of a preparation for oral administration, for example, tablets, capsules, powder, granules, fine granules or dry syrup, the substance ME1207 shows considerably low absorbability compared with the case when administered after meals. It is generally known that a meal is one of factors that affect the absorbability of a drug through the digestive tract (cf. Y. Nakai and M. Hanano, "Seizaigaku (Pharmaceutics)", Nanzando). Namely, meals prolong the gastric emptying time and the absorption site  
 25 passage time of a drug and enhance the acid secretion. Thus, the absorption of the drug is promoted or suppressed depending on the physicochemical and biopharmaceutical properties thereof.

On the other hand, it is known that a fat-soluble cephalosporin compound for oral administration is hardly soluble in water and has an oil/water partition ratio of 100 to 1,000 so that it shows a low  
 30 absorbability through the digestive tract. There are reports with respect to the improvement of the absorbability of the fat-soluble cephalosporin that the addition of cyclodextrins, in particular,  $\alpha$ -cyclodextrin in an amount of approximately 10 to 70 wt% based on the weight of cephalosporin can elevate the water-solubility thereof [cf. JP-A-60-233012 and 62-30713 (the term "JP-A" as used herein means "an unexamined published Japanese patent application") which corresponds to U.S. Patent 4,616,008 or EP-A-  
 35 163433].

SUMMARY OF THE INVENTION

40 An object of the present invention is to enable a cephalosporin compound having an oil/water partition ratio lower than 100 to be absorbed through the digestive tract when orally administered at a hungry state.

In order to achieve the above object, we have conducted extensive studies from the pharmaceutical view point and consequently obtained the following findings.

45 (1) When the substance ME1207 is administered at a hungry state, it shows a poor dispersibility in the empty stomach, which makes its absorbability low.

(2) The dispersibility of the substance ME1207 in the empty stomach and the digestive tract can be improved by adding, to the substance ME1207 having an oil/water partition ratio of about 40 to 60, cyclodextrins, particularly  $\beta$ -cyclodextrin which is hardly soluble in water compared with  $\alpha$ -cyclodextrin and  
 50  $\gamma$ -cyclodextrin, in an amount 1 to 16 parts by weight, preferably 1 to 3 parts by weight, per part by weight of the substance ME1207. Thus, the absorbability of the substance ME1207 can be elevated.

DETAILED DESCRIPTION OF THE INVENTION

In order to improve dispersibility and absorbability of the substance ME1207, the composition of the present invention may further contain, for example, an ionic surfactant such as sodium di-2-ethylhexylsulfosuccinate (OTP-100 NIKKOL®) or sodium lauryl sulfate, a nonionic surfactant such as polyoxyethylene hydrogenated castor oil (HCO-60 NIKKOL®), polyoxyethylene alkyl ether (BL-9EX NIKKOL®) or polyethylene glycol fatty acid ester (MYS-40 NIKKOL®) (the trade names of surfactants as listed above are all products manufactured by Nikko Chemicals) or lecithin which is the major constituent of a biomembrane and has surface activity. These surfactants are added in an amount of approximately 1 to 100 wt%, preferably 2 to 20 wt%, based on the weight of the substance ME1207. Among these, polyethylene glycol fatty acid ester is preferably used in an amount of 2 to 4 wt% based on the weight of the substance ME1207. The substance ME1207 is unstable in an aqueous solution of a pH value of 6 or above. Accordingly, a substance capable of the lowering pH value may be further added with the purpose of preventing the decomposition of the substance ME1207 and improving the absorbability of the same. Examples of these substance include an organic acid such as maleic acid, tartaric acid, citric acid, malic acid or ascorbic acid. These substance may be added in an amount of approximately 10 to 300 wt%, preferably 50 to 150 wt%, based on the weight of the substance ME1207.

The composition of the present invention may further contain a pharmaceutically acceptable binder, vehicle, disintegrating agent, edulcorant, perfume, colorant and/or lubricant. The composition thus obtained may be formulated into, for example, tablets, capsules, powders, granules, fine granules or dry syrups in a conventional manner.

The substance ME1207 thus formulated is administered to a patient in a dose of approximately 50 to 500 mg two or three times per day.

The following Examples and Reference Examples will be given to further illustrate the present invention, but are not construed to limit the scope of the present invention.

#### EXAMPLE 1

130 g of the substance ME1207, 260 g of  $\beta$ -cyclodextrin and 5 g of hydroxypropylmethylcellulose were homogeneously mixed and subjected to wet granulation in a conventional manner. Separately, 60 g of lactose and 6 g of light silicic acid anhydride were homogenized together. These two powders were mixed and 6 g of magnesium stearate was further added thereto. The thus-obtained mixture was tableted in a conventional manner to thereby give tablets each having the following composition.

substance ME1207	130 mg
$\beta$ -cyclodextrin	260 mg
hydroxypropylmethylcellulose	5 mg
lactose	60 mg
light silicic acid anhydride	6 mg
magnesium stearate	6 mg
total	467 mg

#### EXAMPLE 2

130 g of the substance ME1207, 130 g of  $\beta$ -cyclodextrin and 5 g of hydroxypropylmethylcellulose were homogeneously mixed and subjected to wet granulation in a conventional manner. Separately, 10 g of hydroxypropylcellulose of a low degree of substitution and 150 g of citric acid were homogenized together. These two powders were mixed and 6 g of magnesium stearate was further added thereto. The resulting mixture was tableted in a conventional manner to thereby give tablets each having the following composition.

substance ME1207	130 mg
$\beta$ -cyclodextrin	130 mg
hydroxypropylmethylcellulose	5 mg
hydroxypropylcellulose of a low degree of substitution	10 mg
citric acid	150 mg
magnesium stearate	6 mg
total	431 mg

EXAMPLE 3

130 g of the substance ME1207, 130 g of  $\beta$ -cyclodextrin, 5 g of hydroxypropylmethylcellulose and 5 g of sodium di-2-ethylhexylsulfosuccinate were homogeneously mixed and subjected to wet granulation in a conventional manner. Separately, 40 g of hydroxypropylcellulose of a low degree of substitution and 6 g of silicic acid anhydride were homogenized together. These two powders were mixed and 6 g of magnesium stearate was further added thereto. The thus-obtained mixture was tableted in a conventional manner to thereby give tablets each having the following composition.

substance ME1207	130 mg
$\beta$ -cyclodextrin	130 mg
hydroxypropylmethylcellulose	5 mg
sodium di-2-ethylhexylsulfosuccinate	5 mg
hydroxypropylcellulose of a low degree of substitution	40 mg
silicic acid anhydride	6 mg
magnesium stearate	6 mg
total	322 mg

EXAMPLE 4

130 g of the substance ME1207, 200 g of  $\beta$ -cyclodextrin, 26 g of lecithin and 50 g of corn starch were homogeneously mixed and subjected to wet granulation in a conventional manner. Separately, 50 g of lactose and 70 g of succinic acid were homogenized together. These two powders were mixed and 6 g of magnesium stearate was further added thereto. The thus-obtained mixture was tableted in a conventional manner to thereby give tablets each having the following composition.

substance ME1207	130 mg
$\beta$ -cyclodextrin	200 mg
lecithin	26 mg
corn starch	50 mg
lactose	50 mg
succinic acid	70 mg
magnesium stearate	6 mg
total	532 mg

EXAMPLE 5

130 g of the substance ME1207, 130 g of  $\beta$ -cyclodextrin, 5 g of hydroxypropylmethylcellulose and 7 g

of polyoxyethylene hydrogenated castor oil (HCO-60 NIKKOL®) were homogeneously mixed and subjected to wet granulation in a conventional manner. 6 g of magnesium stearate was further added thereto. The resulting mixture was encapsulated in a conventional manner to thereby give capsules each having the following composition.

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substance ME1207	130 mg
$\beta$ -cyclodextrin	130 mg
hydroxypropylmethylcellulose	5 mg
polyoxyethylene hydrogenated castor oil (HCO-60 NIKKOL®)	7 mg
magnesium stearate	6 mg
total	278 mg

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#### EXAMPLE 6

130 g of the substance ME1207, 260 g of  $\beta$ -cyclodextrin, 5 g of hydroxypropylmethylcellulose, 103 g of D-mannitol, 195 g of malic acid and 7 g of polyethylene glycol fatty acid ester (MYS-40 NIKKOL®) were homogeneously mixed. The resulting powder was subjected to wet granulation in a conventional manner and then formulated into fine granules which had the following composition per 700 mg.

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substance ME1207	130 mg
$\beta$ -cyclodextrin	260 mg
hydroxypropylmethylcellulose	5 mg
D-mannitol	103 mg
malic acid	195 mg
polyethylene glycol fatty acid ester (MYS-40 NIKKOL®)	7 mg
total	700 mg

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#### REFERENCE EXAMPLE 1

130 g of the substance ME1207 and 5 g of hydroxypropylmethylcellulose were homogeneously mixed and subjected to wet granulation in a conventional manner. Separately, 60 g of lactose and 6 g of light silicic acid anhydride were homogenized together. These two powders were mixed and 6 g of magnesium stearate was further added thereto. The thus-obtained mixture was tableted in a conventional manner to thereby give tablets each having the following composition.

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substance ME1207	130 mg
hydroxypropylmethylcellulose	5 mg
lactose	60 mg
light silicic acid anhydride	6 mg
magnesium stearate	6 mg
total	207 mg

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#### REFERENCE EXAMPLE 2

130 g of the substance ME1207 and 5 g of hydroxypropylmethylcellulose were homogeneously mixed and subjected to wet granulation in a conventional manner. Separately, 10 g of hydroxypropylcellulose of a

low degree of substitution and 150 g of citric acid were homogenized together. These two powders were mixed and 6 g of magnesium stearate was further added thereto. The mixture thus obtained was tableted in a conventional manner to thereby give tablets each having the following composition.

substance ME1207	130 mg
hydroxypropylmethylcellulose	5 mg
hydroxypropylcellulose of a low degree of substitution	10 mg
citric acid	150 mg
magnesium stearate	6 mg
total	301 mg

### REFERENCE EXAMPLE 3

130 g of the substance ME1207, 5 g of hydroxypropylmethylcellulose and 7 g of polyoxyethylene hydrogenated castor oil (HCO-60 NIKKOL®) were homogeneously mixed and subjected to wet granulation in a conventional manner. 6 g of magnesium stearate was further added thereto. The resulting mixture was encapsulated in a conventional manner to thereby give capsules each having the following composition.

substance ME1207	130 mg
hydroxypropylmethylcellulose	5 mg
polyoxyethylene hydrogenated castor oil (HCO-60 NIKKOL®)	7 mg
magnesium stearate	6 mg
total	148 mg

### TEST EXAMPLE 1

The dispersibility of each preparation obtained in the above Examples 1 through 6 and Reference Examples 1 through 3 was evaluated in the following manner.

#### Test method:

A 200 ml portion of water was charged in each of nine 200 ml Erlenmeyer flasks and maintained at 37° C. Each drug was added to each flask and allowed to stand for 30 minutes. After shaking ten times, it was allowed to stand for additional ten minutes. Then, 1 ml of the suspension 1 cm below its surface was collected with a whole pipette. To the resulting suspension, 1 ml of acetonitrile was added and the drug was completely dissolved. The concentration of the substance ME1207 in the sample was determined by high performance liquid chromatography. When the content of the  $\beta$ -cyclodextrin in the preparation was less than two times as much as the substance ME1207,  $\beta$ -cyclodextrin was preliminarily added to 200 ml of the water so as to equalize the  $\beta$ -cyclodextrin concentrations of all samples.

Table 1 shows the results of the determination of the substance ME1207 concentrations in the suspensions.

Table 1

Sample	Substance ME1207 concentration in suspension ( $\mu\text{g/ml}$ )
Example 1	473.6 $\pm$ 35.1
Example 2	293.0 $\pm$ 22.2
Example 3	393.7 $\pm$ 31.3
Example 4	381.1 $\pm$ 28.0
Example 5	318.9 $\pm$ 39.7
Example 6	532.5 $\pm$ 43.5
Reference Example 1	73.2 $\pm$ 11.2
Reference Example 2	68.5 $\pm$ 9.3
Reference Example 3	35.4 $\pm$ 6.8

TEST EXAMPLE 2

The absorbability of the composition of the invention was evaluated by the following method.

Test method:

Two tablets obtained in the above Example 1 and Reference Example 3 and 1.4 g of granules obtained in example 6, each containing 260 mg of the substance ME1207, were orally administered to each of 6 female beagles weighing approximately 10 kg together with 30 ml of water. 0.25, 0.5, 1, 2, 4, 6 and 8 hours after the administration, the concentration of the substance ME1207 in the plasma of each animal was determined by high performance liquid chromatography and the area under the plasma drug concentration curve (AUC) was calculated by the trapezoidal method. These three preparations were administered after fasting for 24 hours and 30 minutes after meals according to the protocol defined in Table 2. A rest time of two weeks was provided between test periods.

Table 2

Administration schedule						
Animal No.	1st	2nd	3rd	4th	5th	6th
1	a	(b)	c	(a)	b	(c)
2	(a)	b	(c)	a	(b)	c
3	b	(c)	a	(b)	c	(a)
4	(b)	c	(a)	b	(c)	a
5	c	(a)	b	(c)	a	(b)
6	(c)	a	(b)	c	(a)	b
Note:	a: Preparation of Example 1 b: Preparation of Example 6 c: Preparation of Reference Example 3 ( ): Administered at a hungry state					

Table 3 shows the concentrations of the substance ME1207 in plasma and AUC in the case of the administration at a hungry state, and Table 4 shows those in the case of the administration after meals.

Table 3

Sample	Substance ME1207 concentration ( $\mu\text{g/ml}$ )							AUC ( $\mu\text{g/ml}\cdot\text{hr}$ )
	0.25 (hr)	0.50 (hr)	1.00 (hr)	2.00 (hr)	4.00 (hr)	6.00 (hr)	8.00 (hr)	
Example 1	0.71 (0.31)	1.73 (0.26)	2.34 (0.19)	1.79 (0.08)	0.40 (0.11)	0.22 (0.05)	0.10 (0.05)	6.59 (0.68)
Example 6	0.91 (0.35)	1.97 (0.37)	2.55 (0.38)	1.96 (0.45)	0.52 (0.14)	0.29 (0.11)	0.14 (0.04)	7.58 (1.28)
Reference Example 3	0.03 (0.02)	0.14 (0.06)	0.05 (0.01)	0.02 (0.01)	0.01 (0.00)	0.00 (0.00)	0.00 (0.00)	0.15 (0.04)

Note: The value of upper line is a mean value, while the parenthetic value of lower line is S.E.

Table 4

Sample	Substance ME1207 concentration ( $\mu\text{g/ml}$ )							AUC ( $\mu\text{g/ml}\cdot\text{hr}$ )
	0.25 (hr)	0.50 (hr)	1.00 (hr)	2.00 (hr)	4.00 (hr)	6.00 (hr)	8.00 (hr)	
Example 1	0.52 (0.08)	1.61 (0.21)	2.49 (0.18)	1.91 (0.14)	0.41 (0.06)	0.30 (0.04)	0.10 (0.03)	6.97 (0.60)
Example 6	0.60 (0.18)	1.50 (0.27)	2.39 (0.18)	2.20 (0.20)	0.40 (0.08)	0.28 (0.07)	0.10 (0.03)	7.25 (0.76)
Reference Example 3	1.06 (0.08)	2.10 (0.18)	2.46 (0.08)	1.73 (0.06)	0.45 (0.09)	0.23 (0.06)	0.08 (0.03)	6.91 (0.42)

Note: The value of upper line is a mean value, while the parenthetic value of lower line is S.E.

As is apparent from the results shown in Tables 3 and 4, the compositions according to the present invention provide the elevated absorbability of the substance ME1207 in the case of oral administration at a hungry state to a level comparable to that in the case of administration after meals. Thus, the availability of the substance ME1207 is highly improved.

While the invention has been described in detail and with reference to specific examples thereof, it will be apparent to one skilled in the art that various changes and modifications can be made therein without departing from the spirit and scope thereof.

### Claims

1. An antibacterial composition for oral administration comprising pivaloyloxymethyl-(6R,7R)-7[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyiminoacetamide]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]cephem-4-carboxylate (hereinafter referred to as the substance ME1207),  $\beta$ -cyclodextrin and a pharmaceutically acceptable carrier.

2. The antibacterial composition according to claim 1, wherein said  $\beta$ -cyclodextrin is contained in an amount of 1 to 16 parts by weight per part by weight of the substance ME1207.

3. The antibacterial composition according to claim 1, wherein said  $\beta$ -cyclodextrin is contained in an amount of 1 to 3 parts by weight per part by weight of the substance ME1207.

4. The antibacterial composition according to claim 1, which contains a surfactant selected from the group consisting of sodium di-2-ethylhexylsulfosuccinate, sodium lauryl sulfate, polyoxyethylene hydrogenated castor oil, polyoxyethylene alkyl ether, polyethylene glycol fatty acid ester and lecithin.

5. The antibacterial composition according to claim 4, wherein said surfactant is contained in an amount of approximately 1-100 wt% based on the weight of the substance ME1207.



6. The antibacterial composition according to claim 1, which contains a substance capable of lowering pH value selected from the group consisting of maleic acid, tartaric acid, citric acid, succinic acid, malic acid and ascorbic acid.

7. The antibacterial composition according to claim 6, wherein said substance is contained in an amount of approximately 10 to 300 wt% based on the weight of the substance ME1207.

Claims for the following Contracting State: ES

10 1. The use of a composition for oral administration comprising pivaloyloxymethyl-(6R,7R)-7[(Z)-2-(2-aminothiazol-4-yl)-2-methoxyimino-acetamide]-3-[(Z)-2-(4-methylthiazol-5-yl)ethenyl]cephem-4-carboxylate,  $\beta$ -cyclodextrin and a pharmaceutically acceptable carrier for the manufacture of a medicament for the treatment and/or prevention of bacterial infectious diseases.

2. The use of a composition according to claim 1, wherein said  $\beta$ -cyclodextrin is contained in an amount of 1 to 16 parts by weight per part by weight of the substance ME1207.

3. The use of a composition according to claim 1, wherein said  $\beta$ -cyclodextrin is contained in an amount of 1 to 3 parts by weight per part by weight of the substance ME1207.

4. The use of a composition according to claim 1, which contains a surfactant selected from the group consisting of sodium di-2-ethylhexylsulfosuccinate, sodium lauryl sulfate, polyoxyethylene hydrogenated castor oil, polyoxyethylene alkyl ether, polyethylene glycol fatty acid ester and lecithin.

5. The use of a composition according to claim 4, wherein said surfactant is contained in an amount of approximately 1-100 wt% based on the weight of the substance ME1207.

6. The use of a composition according to claim 1, which contains a substance capable of lowering pH value selected from the group consisting of maleic acid, tartaric acid, citric acid, succinic acid, malic acid and ascorbic acid.

7. The use of a composition according to claim 6, wherein said substance is contained in an amount of approximately 10 to 300 wt% based on the weight of the substance ME1207.



Europäisches Patentamt  
European Patent Office  
Office européen des brevets

Publication number:

**0 339 465  
A3**

(1)

## EUROPEAN PATENT APPLICATION

(2) Application number: 89107040.1

(51) Int. Cl.<sup>5</sup>: **A61K 31/545 , A61K 31/715 ,  
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(22) Date of filing: 19.04.89

(30) Priority: 19.04.88 JP 94543/88

(43) Date of publication of application:  
02.11.89 Bulletin 89/44

(84) Designated Contracting States:  
**AT BE CH DE ES FR GB IT LI NL SE**

(58) Date of deferred publication of the search report:  
28.03.90 Bulletin 90/13

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European Patent  
Office

# EUROPEAN SEARCH REPORT

Application Number

EP 89 10 7040

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
D,A	EP-A-0 163 433 (TAKEDA CHEMICAL INDUSTRIES, LTD) -----	1-7	A 61 K 31/545 A 61 K 31/715 C 08 B 37/00 // (A 61 K 31/715 A 61 K 31:545)
			TECHNICAL FIELDS SEARCHED (Int. Cl.4)
			A 61 K C 08 B
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 13-12-1989	Examiner BRINKMANN C.
<b>CATEGORY OF CITED DOCUMENTS</b> X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons ..... & : member of the same patent family, corresponding document			